

WHAT IS CLAIMED:

1. A method of treating pathogen infection in a subject, said method comprising:
5 inhibiting proteasomal activity in a pathogen under conditions effective to make the pathogen susceptible to antibacterial host defenses, thereby treating a pathogen infection in the subject.
2. The method according to claim 1, wherein the proteasomal activity
10 is an AAA ATPase activity or a proteasomal protease activity.
3. The method according to claim 2, wherein the proteasomal activity is proteasomal protease activity in a proteasome core.
4. The method according to claim 3, wherein the protease is a product
15 of *prcBA* genes.
5. The method according to claim 4, wherein the protease is PrcA.
6. The method according to claim 4, wherein the protease is PrcB.
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7. The method according to claim 2, wherein the proteasomal activity is an AAA ATPase activity where the AAA ATPase is selected from the group consisting of an AAA ATPase forming ring-shaped complex, a proteasome associated nucleotidase,
25 a mycobacterial proteasome ATPase, and a proteasome accessory factor.
8. The method according to claim 7, where the AAA ATPase is an AAA ATPase forming ring-shaped complex.
9. The method according to claim 8, wherein AAA ATPase forming
30 ring-shaped complex is a product of a *groEL1* gene.

10. The method according to claim 9, where the groEL gene product is a groEL protein.

11. The method according to claim 8, wherein the AAA ATPase
5 forming ring-shaped complex is a product of a Rv2115c gene.

12. The method according to claim 1, wherein the host defense is oxidative/nitrosative stress.

13. The method according to claim 12, wherein the
10 oxidative/nitrosative stress is reactive nitrogen intermediate-induced stress.

14. The method according to claim 12, wherein the
oxidative/nitrosative stress is reactive oxygen intermediate-induced stress.

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15. The method according to claim 1, wherein the inhibiting is carried out by administering an inhibitor of proteasomal activity.

16. The method according to claim 15, wherein the administering is
20 oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, or intranasal.

17. The method according to claim 15, wherein the inhibitor of proteasomal activity is selected from the group consisting of epoxomicin and N-[4-morpholine]carbonyl- β -[1-naphthyl]-L-alanine-L-leucine boronic acid.

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18. The method according to claim 1, wherein the pathogen is selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and another disease-causing *Mycobacterium*.

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19. The method according to claim 1, wherein the subject is a mammal.

20. The method according to claim 19, wherein the mammal is human.

21. A method of treating pathogen infection in a subject, said method comprising:

inhibiting enzyme activity in a pathogen under conditions effective
5 to make the pathogen susceptible to antibacterial host defenses, wherein the enzyme is selected from the group consisting of a DNA repair enzyme and a flavin-like co-factor synthesis enzyme.

22. The method according to claim 21, wherein the enzyme is a DNA
10 repair enzyme in the form of a nucleotidase excision-repair enzyme.

23. The method according to claim 22, wherein the nucleotidase excision-repair enzyme is a product of a *uvr* gene family.

24. The method according to claim 23, wherein the nucleotidase excision-repair enzyme is UvrB.

25. The method according to claim 21, wherein the enzyme is a flavin-like co-factor synthesis enzyme.

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26. The method according to claim 21, wherein the host defense is oxidative/nitrosative stress.

27. The method according to claim 26, wherein the
25 oxidative/nitrosative stress is reactive nitrogen intermediate-induced stress.

28. The method according to claim 26, wherein the oxidative/nitrosative stress is reactive oxygen intermediate-induced stress.

29. The method according to claim 21, wherein the inhibiting is carried
30 out by administering an inhibitor of the enzyme activity.

30. The method according to claim 29, wherein the administering is oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, or intranasal.

31. The method according to claim 21, wherein the pathogen is
5 selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and another disease-causing *Mycobacterium*

32. The method according to claim 21, wherein the subject is a
mammal.

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33. The method according to claim 32, wherein the mammal is human.

34. A method of screening a known or suspected proteasomal inhibitor
compound for an ability to sensitize bacteria to antibacterial effects of
15 oxidative/nitrosative stress comprising:

growing bacteria in a medium containing an exogenous stress-
inducing agent under conditions effective to induce oxidative/nitrosative stress in the
bacteria;

20 adding a known or suspected proteasomal inhibitor compound to
the medium; and

determining whether the bacteria survive or fail to survive, wherein
the failure to survive indicates an ability of the inhibitor compound to sensitize the
bacteria to antibacterial effects of oxidative/nitrosative stress.

25 35. The method according to claim 34, wherein the
oxidative/nitrosative stress is reactive nitrogen intermediate-induced stress.

36. The method according to claim 34, wherein the
oxidative/nitrosative stress is reactive oxygen intermediate-induced stress.

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37. The method according to claim 34, wherein the stress-inducing
agent is a nitrite.

38. The method according to claim 34, wherein the proteasomal inhibitor compound inhibits AAA ATPase activity.

5 39. The method according to claim 38, wherein the AAA ATPase is selected from the group consisting of an AAA ATPase forming ring-shaped complex, a proteasome associated nucleotidase, a mycobacterial proteasome ATPase, and a proteasome accessory factor.

10 40. The method according to claim 39, wherein the AAA ATPase is an AAA ATPase forming ring-shaped complex.

41. The method according to claim 40, wherein AAA ATPase forming ring-shaped complex is a product of a groEL1 gene.

15 42. The method according to claim 41, where the groEL gene product is a groEL protein.

20 43. The method according to claim 40, wherein the AAA ATPase forming ring-shaped complex is a product of an Rv2115c gene.

44. The method according to claim 34, wherein the proteasomal inhibitor compound inhibits protease activity.

25 45. The method according to claim 44, wherein the protease is produced in a proteasomal core.

46. The method according to claim 45, wherein the protease is a product of *prcBA* genes.

30 47. The method according to claim 46, wherein the protease is PrcA.

48. The method according to claim 46, wherein the protease is PrcB.

49. The method according to claim 34, wherein the bacteria is selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and another disease-causing *Mycobacterium*.

5 50. A method of screening a known or suspected DNA repair enzyme inhibitor compound for an ability to sensitize bacteria to antibacterial effects of oxidative/nitrosative stress comprising:

growing bacteria in a medium containing an exogenous stress-inducing agent under conditions to induce oxidative/nitrosative stress in the bacteria;

10 adding a known or suspected DNA repair enzyme inhibitor compound to the medium; and

determining whether the bacteria survive or fail to survive, wherein the failure to survive indicates the ability of the inhibitor compound to sensitize bacteria to antibacterial effects of oxidative/nitrosative stress.

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51. The method according to claim 50, wherein the oxidative/nitrosative stress is reactive nitrogen intermediate-induced stress.

20 52. The method according to claim 50, wherein the oxidative/nitrosative stress is reactive oxygen intermediate-induced stress.

53. The method according to claim 50, wherein the stress-inducing agent is a nitrite.

25 54. The method according to claim 50, wherein the DNA repair enzyme is a nucleotidase excision-repair enzyme.

55. The method according to claim 54, wherein the nucleotidase excision-repair enzyme is a product of a *uvr* gene family.

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56. The method according to claim 55, wherein the nucleotidase excision-repair enzyme is UvrB.

57. The method according to claim 50, wherein the bacteria is selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and another disease-causing *Mycobacterium*.

5 58. A method of screening a known or suspected flavin-like co-factor synthesis enzyme inhibitor compound for an ability to sensitize bacteria to antibacterial effects of oxidative/nitrosative stress comprising:

growing bacteria in a medium containing an exogenous stress-inducing agent under conditions effective to induce oxidative/nitrosative stress in the
10 bacteria;

adding a known or suspected flavin-like co-factor synthesis enzyme inhibitor compound to the medium; and

determining whether the bacteria survive or fail to survive, wherein the failure to survive indicates the ability of the inhibitor compound to sensitize bacteria
15 to antibacterial effects of oxidative/nitrosative stress.

59. The method according to claim 58, wherein the oxidative/nitrosative stress is reactive nitrogen intermediate-induced stress.

20 60. The method according to claim 58, wherein the oxidative/nitrosative stress is reactive oxygen intermediate-induced stress.

61. The method according to claim 58, wherein the stress-inducing agent is a nitrite.
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62. The method according to claim 58, wherein the bacteria is *Mycobacterium tuberculosis*, *Mycobacterium leprae*, or another disease-causing *Mycobacterium*.

30 63. A method of treating pathogen infection in a subject, said method comprising:

inhibiting proteasomal activity in a pathogen under conditions effective to make the pathogen susceptible to antibacterial host defenses and

inhibiting enzyme activity in the pathogen under conditions effective to make the pathogen susceptible to antibacterial host defenses, thereby treating the pathogen infection in a host.

5 64. The method according to claim 63, wherein the proteosomal activity is an AAA ATPase activity or a protease activity.

 65. The method according to claim 64, wherein the proteasomal activity is protease activity where a proteasomal core is being inhibited.

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 66. The method according to claim 65, wherein the protease is a product of the *prcBA* gene.

 67. The method according to claim 66, wherein the protease is PrcB.

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 68. The method according to claim 66, wherein the protease is PrcA.

 69. The method according to claim 64, wherein the proteasomal activity is an AAA ATPase activity, where the AAA ATPase is selected from the group consisting of an AAA ATPase forming ring-shaped complex, a proteasome associated nucleotidase, a mycobacterial proteasome ATPase, and a proteasome accessory factor.

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 70. The method according to claim 69, wherein the AAA ATPase is an AAA ATPase forming ring-shaped complex.

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 71. The method according to claim 70, wherein the AAA ATPase forming ring-shaped complex is a product of a *groEL1* gene.

 72. The method according to claim 71, where the *groEL* gene product is a *groEL* protein.

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 73. The method according to claim 70, wherein the AAA ATPase forming ring-shaped complex is a product of an *Rv2115c* gene.

74. The method according to claim 63, wherein the inhibiting is carried out by administering an inhibitor of proteasomal activity.

5 75. The method according to claim 74, wherein the inhibitor of proteasomal activity is selected from the group consisting of epoxomicin and N-[4-morpholine]carbonyl- β -[1-naphthyl]-L-alanine-L-leucine boronic acid.

76. The method according to claim 74, wherein the administering is
10 oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, or intranasal.

77. The method according to claim 63, wherein the enzyme is selected from the group consisting of a DNA repair enzyme and a flavin-like co-factor synthesis enzyme.
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78. The method according to claim 77, wherein the enzyme inhibited is a DNA repair enzyme in the form of a nucleotidase excision-repair enzyme.

79. The method according to claim 78, wherein the nucleotidase
20 excision-repair enzyme is a product of a *uvr* gene family.

80. The method according to claim 79, wherein the nucleotidase excision-repair enzyme is UvrB.

25 81. The method according to claim 77, wherein the enzyme inhibited is a flavin-like co-factor synthesis enzyme.

82. The method according to claim 63, wherein the host defense is oxidative/nitrosative stress.
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83. The method according to claim 82, wherein the oxidative/nitrosative stress is reactive nitrogen intermediate-induced stress.

84. The method according to claim 82, wherein the oxidative/nitrosative stress is reactive oxygen intermediate-induced stress.

85. The method according to claim 63, wherein the pathogen is selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and another disease-causing *Mycobacterium*.

86. The method according to claim 63, wherein the subject is a mammal.

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87. The method according to claim 86, wherein the mammal is human.

88. A method of screening a proteasomal inhibitor test compound for an ability to sensitize bacteria to the antibacterial effects of oxidative/nitrosative stress, said method comprising:

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providing an isolated protein having proteasomal activity;
providing a reagent upon which the isolated protein exerts activity;
providing a proteasomal inhibitor test compound;
blending the protein, the reagent, and the test compound to form a

20 mixture;

determining the activity of the protein upon the reagent in the mixture; and

measuring any difference between the activity of the protein upon the reagent with and without the test compound, thereby screening the test compound for an ability to sensitize bacteria to the antibacterial effects of oxidative/nitrosative stress.

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89. The method according to claim 88, wherein the proteasomal inhibitor compound inhibits AAA ATPase activity.

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90. The method according to claim 89, wherein the AAA ATPase is selected from the group consisting of an AAA ATPase forming ring-shaped complex, a proteasome associated nucleotidase, a mycobacterial proteasome ATPase, and a proteasome accessory factor.

91. The method according to claim 90, wherein the AAA ATPase is an AAA ATPase forming ring-shaped complex.

5 92. The method according to claim 91, wherein AAA ATPase forming ring-shaped complex is a product of a *groEL1* gene.

93. The method according to claim 92, where the *groEL* gene product is a *groEL* protein.
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94. The method according to claim 91, wherein the AAA ATPase forming ring-shaped complex is a product of an *Rv2115c* gene.

95. The method according to claim 88, wherein the proteasomal inhibitor compound inhibits protease activity.
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96. The method according to claim 95, wherein the protease is produced in a proteasomal core.

20 97. The method according to claim 96, wherein the protease is a product of *prcBA* genes.

98. The method according to claim 97, wherein the protease is *PrcA*.

25 99. The method according to claim 97, wherein the protease is *PrcB*.

100. The method according to claim 97, wherein the protease is *protease1*.

30 101. The method according to claim 88, wherein the isolated protein is a bacterial protein.

102. The method according to claim 101, wherein the bacteria is selected from consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and another disease-causing *Mycobacterium*.